Claims 45 and 48 were amended. Appendix A provides the version with markings to show change. Appendix B shows all pending claims currently under examination.

Objection to the specification

The specification was objected to as reciting an embedded hyperlink at page 14. Applicants have amended the specification to delete this link. Applicants respectfully request that the objection be withdrawn.

Objection to the claims

Claim 45 was objected to for improperly depending on non-elected claim 41. Claim 45 has been amended to incorporate the elements of claim 41. Applicants therefore respectfully request that the objection be withdrawn.

Rejection: double patenting

Claims 11, 12, and 45-50 were rejected as allegedly obvious under the judicially created doctrine of obviousness type double patenting. Applicants request that the rejection be held in abeyance while an executed terminal disclaimer is being obtained. Applicants will submit the executed terminal disclaimer to the PTO at the earliest opportunity.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 48 was rejected as allegedly indefinite for reciting improper antecedent basis. The claim has been amended to correct the antecedent basis. Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: written description and enablement

Claim 63 was rejected as allegedly lacking written description, and claim 64 was rejected as allegedly lacking enablement. As these claims have been canceled without prejudice to subsequent prosecution, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please amend the specification on page 13, line 26 to page 14, line 6 as follows:

A preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al., Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul *et al., J. Mol. Biol.* 215:403-410 (1990), respectively. BLAST and BLAST 2.0 are used, with the default parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information [(http://www.ncbi.nlm.nih.gov/)]. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

IN THE CLAIMS

45. (once amended) A method of increasing the mutation rate of a virus in an animal comprising administering to the animal a therapeutically effective dose of a mutagenic ribonucleoside analog composition [of claim 41], wherein the analog is one that in a infected cell with a virus of interest is incorporated by a polymerase into an RNA copy of a genomic nucleic acid encoding the virus, said analog replacing a first natural occurring nucleotide having a first complementary nucleotide wherein said analog complements a second nucleotide which is other than the first nucleotide together with a pharmaceutically acceptable carrier.

APPENDIX B

PENDING CLAIMS

1. A method of increasing the mutation rate of a virus, comprising administering an RNA nucleoside analog to a virally infected cell, wherein the analog is incorporated by a polymerase into an RNA copy of a genomic nucleic acid encoding the virus, said analog replacing a first natural occurring nucleotide having a first complementary nucleotide wherein said analog complements a second nucleotide which is other than the first nucleotide, thereby inducing the virus to mutate.

2. The method of claim 1, wherein the RNA nucleoside analog replaces uracil.

3. The method of claim 1, wherein the RNA nucleoside analog replaces adenine.

4. The method of claim 1, wherein the RNA nucleoside analog replaces cytidine.

5. The method of claim 1, wherein the RNA nucleoside analog replaces guanine.

6. The method of claim 1, wherein the RNA nucleoside analog is incorporated by the polymerase into the RNA copy of the genomic nucleic acid with an efficiency at least about 0.1% that of a naturally occurring complementary nucleic acid.

7. The method of claim 1, wherein the method further includes the proviso that the RNA nucleoside analog is not ribavirin or a 5-halo analog of 1-â-D-ribofuranosylimidazole-4-carboxamide.

8. The method of claim 1, wherein the RNA analog is a non-chain terminating analog.

9. The method of claim 1, wherein the method further includes the proviso that if the virus is HIV, then the RNA nucleoside analog is not HEPT or a 2',5'-bis-O-sialylated-3'-spiro-

substituted (TSAO) adenine, hypoxanthine, N^1-alkyl-hypoxanthine, or xanthine or a nucleoside analog that is incorporated and extended at high efficiency by reverse transcriptase of HIV.

10. The method of claim 1, wherein the nucleoside analog is selected from the group consisting of N^4-aminocytidine, N^1-methyl-N^4-aminocytidine, 3,N^4-ethenocytidine, 3-methylcytidine, 5-hydroxycytidine, N^4-dimethylcytidine, 5-(2-hydroxyethyl)cytidine, 5-chlorocytidine, 5-bromocytidine, N^4-methyl-N^4-aminocytidine, 5-aminocytidine, 5-nitrosocytidine, 5-(hydroxyalkyl)-cytidine, 5-(thioalkyl)-cytidine and cytidine glycol, 5-hydroxyuridine, 3-hydroxyethyluridine, 3-methyluridine, O^2-methyluridine, O^2-ethyluridine, 5-aminouridine, O^4-methyluridine, O^4-ethyluridine, O^4-isobutyluridine, O^4-alkyluridine, 5-nitrosouridine, 5-(hydroxyalkyl)-uridine, and 5-(thioalkyl)-uridine, 1,N^6-ethenoadenosine, 3-methyladenosine, and N^6-methyladenosine, 8-hydroxyguanosine, O^6-methylguanosine, O^6-ethylguanosine, O^6-isopropylguanosine, 3,N^2-ethenoguanosine, 0^6-alkylguanosine, 8-oxo-guanosine, 2,N^3-ethenoguanosine, and 8-aminoguanosine.

11. The method of claim 1, wherein the virus is a retrovirus or a flavivirus.

12. The method of claim 11, wherein the virus is a pestivirus.

13. The method of claim 1, wherein the polymerase is a human polymerase II.

14. The method of claim 1, wherein the cell is in cell culture.

15. The method of claim 1, wherein the cell is in an animal.

16. The method of claim 1, wherein increasing the mutation rate of the virus produces a progressive loss of viability of the virus.

17. The method of claim 1, comprising administration of more than one species of RNA nucleoside analog to the virally infected cell.

18. The method of claim 1, wherein the virus is an RNA virus selected from the group consisting of hepatitis C, coronavirus, influenza, respiratory syncytial virus, BVDV, and dengue fever.

45. (once amended) A method of increasing the mutation rate of a virus in an animal comprising administering to the animal a therapeutically effective dose of a mutagenic ribonucleoside analog composition wherein the analog is one that in a infected cell with a virus of interest is incorporated by a polymerase into an RNA copy of a genomic nucleic acid encoding the virus, said analog replacing a first natural occurring nucleotide having a first complementary nucleotide wherein said analog complements a second nucleotide which is other than the first nucleotide together with a pharmaceutically acceptable carrier.

46. The method of claim 45, wherein the nucleoside analog is selected from the group consisting of N^4-aminocytidine, N^1-methyl-N^4-aminocytidine, 3,N^4-ethenocytidine, 3-methylcytidine, 5-hydroxycytidine, N^4-dimethylcytidine, 5-(2-hydroxyethyl)cytidine, 5-chlorocytidine, 5-bromocytidine, N^4-methyl-N^4-aminocytidine, 5-aminocytidine, 5-nitrosocytidine, 5-(hydroxyalkyl)-cytidine, 5-(thioalkyl)-cytidine and cytidine glycol, 5-hydroxyuridine, 3-hydroxyethyluridine, 3-methyluridine, O^2-methyluridine, O^2-ethyluridine, 5-aminouridine, O^4-methyluridine, O^4-ethyluridine, O^4-isobutyluridine, O^4-alkyluridine, 5-nitrosouridine, 5-(hydroxyalkyl)-uridine, and 5-(thioalkyl)-uridine, 1,N^6-ethenoadenosine, 3-methyladenosine, and N^6-methyladenosine, 8-hydroxyguanosine, O^6-methylguanosine, O^6-ethylguanosine, O^6-isopropylguanosine, 3,N^2-ethenoguanosine, 0^6-alkylguanosine, 8-oxo-guanosine, 2,N^3-ethenoguanosine, and 8-aminoguanosine.

47. The method of claim 45, wherein the RNA nucleoside analog is incorporated by a polymerase present in virally infected cells of the animal into an RNA copy of a genomic nucleic acid of the virus with an efficiency at least about 0.1% that of a naturally occurring complementary nucleic acid.

48. (once amended) The method of claim 45, wherein the animal is a human patient infected with the virus selected from the group consisting of HIV-1, HIV-2, HTLV-1, HTLV-2, hepatitis A, hepatitis B, hepatitis C, and dengue fever virus.

49. The method of claim 45, wherein the animal is a human patient having a disease selected from the group consisting of AIDS, hepatitis B, hepatitis C, T-cell leukemia.

50. The method of claim 45, the animal having a disease selected from the group consisting of feline leukemia virus, feline immunodeficiency virus, BVDV, or vesicular stomatitis virus.

66. The method of claim 1, wherein the RNA nucleoside analog is an enantio-specific nucleoside analog.